Concise report

Does achieving clinical response prevent work stoppage or work absence among employed patients with early rheumatoid arthritis?

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Abstract

Objectives. To evaluate the impact of clinical response on work stoppage or work absence among employed people with early RA.

Methods. First-year data from the combination of MTX and etanercept trial was used. The analyses were restricted to the 205 patients working full or part time at baseline who answered questions on whether they stopped working or missed days from work in one or more of the four follow-up visits. Work stoppage referred to the first occurrence of subjects reporting stopping work. Work absence was defined as whether patients reported missed days from work. Clinical response and activity state considered included the ACR and European League against Rheumatism response criteria, 28-joint DAS (DAS-28) remission and the minimum clinically important difference of the HAQ score.

Results. After adjustment for baseline characteristics, ACR70 responders were 72% less likely to stop working and 55% less likely to miss work than ACR20 non-responders (P < 0.05). Patients achieving DAS-28 remission were 54% less likely to stop work than those with DAS-28 > 3.2 (P < 0.05). Moderate improvements did not appear to effect work stoppage or missed days after adjustments.

Conclusions. Results suggest that achieving clinical remission or major improvement might be necessary to significantly impact work outcomes.

Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00195494.

Key words: early rheumatoid arthritis, absenteeism, work outcomes, clinical response, remission.

Introduction

Numerous clinical trials in patients with early RA have demonstrated that early intervention with biologics reduces the signs and symptoms of RA, improves physical function and inhibits radiographic progression, and a greater proportion of patients achieve clinical remission or major response compared with MTX [1–5]. Furthermore, studies have found that these treatments lead to positive work-related outcomes among RA patients. Compared with a single therapy with MTX, early interventions with a combination of biologic therapy with MTX significantly reduced absent workdays of employed early RA patients and maintained their employment potential [3, 6–8].

Despite the growing evidence of the benefits of early aggressive treatment, the link between response to treatment and work-related outcomes among patients with RA has not been fully evaluated. Zhang et al. [9] suggested that biologic DMARDs could improve presenteeism and unpaid work productivity because they induced higher clinical response. According to the ACR improvement criterion (ACR20) and the minimum clinically important difference (MCID) of the HAQ score, Osterhaus et al. [10] found that responders reported significantly higher reductions in missed workdays over 24 weeks than non-responders. Another study conducted by Halpern et al. [11] had found...
that patients who achieved the ACR20, ACR50, ACR70, good response to the European League against Rheumatism (EULAR) criteria and 28-joint DAS (DAS-28) remission were less likely to stop working. The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial has shown the association between treatment response and work capacity (cumulative number of days of sick leave and RA-related permanent work disability over a 5-year follow-up) in early RA [12].

Given the limited evidence and the fact that most results were observed in patients with long-standing RA, it is of interest to further identify whether the association between achievement of clinical response and work-related outcomes holds among patients with early-active RA receiving different treatments. Therefore, the objective of this study was to evaluate the impact of response to treatment or achieving a certain disease activity state on work stoppage and work absence among patients with early RA.

Methods

Study population

We used first-year data from the combination of MTX and etanercept (COMET) trial, a double-blind, randomized, parallel-group, multicentre, outpatient study, where 542 patients were randomized to two treatment groups: a combination of etanercept (ETN) and MTX vs MTX alone [1, 6]. The main inclusion criteria were: (i) ≥ 18 years of age; (ii) met the ACR criteria for diagnosis of RA; (iii) disease duration was between 3 months and 2 years; and (iv) had a DAS-28 ≥ 3.2 and at least one of the following two criteria: ESR ≥ 28 mm/h or CPR level ≥ 20 mg/l. The study complied with the Declaration of Helsinki, and received institutional review board approval and regulatory review before site initiation. All subjects provided written informed consent.

Outcome measures

In the COMET trial, patients reported whether they stopped working or missed days from work because of their health at Weeks 12, 24, 36 and 52. Patients responded to questions at Weeks 12 and 24 for the prior 4-week period, and at Weeks 36 and 52 for the prior 8-week period. In the current study, work stoppage at each visit was coded as a dummy variable and was evaluated until patients’ first occurrence of stopping work or 52 weeks. Work absence at each visit was defined as whether any missed work was reported and all responses over the entire study period were included in our analysis. As the questionnaires regarding stopping work and missing work were asked separately in the trial, the two outcome measures here were treated independently.

Response criteria and disease activity state

ACR20, ACR50 and ACR70 responses were defined according to the ACR definition of improvement [13]. Four response levels were also defined according to ACR response criteria: no ACR20 response, ACR20–ACR50, ACR50–ACR70 and ACR70. EULAR response criteria were also considered [14, 15]. For disease activity state, we categorized DAS-28 into three categories: >3.2, 2.6–3.2, <2.6. A DAS-28 < 2.6 was defined as clinical remission [15, 16]. HAQ score difference of 0.22 was used to represent the MCID [17, 18].

Analyses

The analyses were restricted to patients working full or part time at baseline and those who answered questions on whether they stopped working or missed days from work in one or more of the four follow-up visits. For each response criterion, a separate logistic generalized estimating equations (GEEs) model for repeated measures was used for both unadjusted and adjusted analyses. In order to examine the adjusted association, in each model, we included the response variable as the independent variable of interest and patients’ demographics [age, gender, ethnicity and working status (full vs part time)] and treatment (ETN + MTX vs MTX) as fixed covariates. Patients’ baseline clinical and quality of life outcomes were also selected in each model for adjustment according to the selection criterion: quasi-likelihood under the independence model criterion (QIC) [19].

Results

In total, 214 patients from 22 countries were working full or part time at baseline. Of them, 205 answered questions on whether they stopped working or missed days from work in any of the four follow-up visits, and thus were included in our analysis. Their mean age was 45 years, 69% were female and RA duration was 8.7 months [6]. At baseline, patients had high levels of disease activity, pain and fatigue, moderate-to-severe functional disability and poor quality of life.

Table 1 shows that 8.5, 5.4, 3.3 and 1.4% of patients stopped working during the 0–12, 12–24, 24–36 and 36–52 weeks, respectively. Correspondingly, 18.5, 18.8, 16.5 and 14.8% of patients reported that they had ever missed work, which suggests that the occurrence of work absence decreased over the treatment time. On the other hand, the number of responders increased. For example, the proportion of patients achieving ACR70 was 27.0, 39.7, 46.1 and 46.6% at Weeks 12, 24, 36 and 52, respectively, and the proportion of patients achieving good EULAR response was 39.5, 56.6, 59.0 and 65.4%, respectively.

The unadjusted analysis results show that employed patients with early RA achieving clinical response were less likely to stop work or miss work (Table 2). However, after adjustment for baseline characteristics and treatment, the association was significant only among patients who achieved ACR70 and DAS-28 remission. Compared with ACR20 non-responders, patients achieving ACR70 were 72% less likely to stop working and 55% less likely to miss work. Patients achieving DAS-28 remission (<2.6) were 54% less likely to stop work than those with DAS-28 > 3.2. As an adjustment variable included in the GEE analysis, treatment with ETN + MTX was associated with reduced likelihood of work stoppage or absence than treatment with MTX (data not shown).
Discussion

The relationship between clinical response and work-related outcomes was dependent on the specific clinical outcome measure considered. After controlling for baseline characteristics and treatment, only a very high response (ACR70) and DAS-28 remission was shown to be associated with a significant lower likelihood of stopping work or missing work. This suggests that a mild or moderate clinical improvement among employed early RA patients tabletops.

### Table 1: Frequency of work stoppage, work absence and achievement of clinical responses by weeks

<table>
<thead>
<tr>
<th>Variables</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work stoppage</td>
<td>17 (8.5)</td>
<td>9 (5.4)</td>
<td>5 (3.3)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Work absence</td>
<td>37 (18.5)</td>
<td>34 (18.8)</td>
<td>29 (16.5)</td>
<td>24 (14.8)</td>
</tr>
<tr>
<td>Missed days/week, mean (s.d.)</td>
<td>0.61 (1.51)</td>
<td>0.41 (1.15)</td>
<td>0.29 (0.91)</td>
<td>0.20 (0.72)</td>
</tr>
<tr>
<td>ACR response criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>141 (69.1)</td>
<td>160 (78.4)</td>
<td>169 (82.8)</td>
<td>168 (82.4)</td>
</tr>
<tr>
<td>ACR50</td>
<td>97 (47.5)</td>
<td>125 (61.3)</td>
<td>137 (67.2)</td>
<td>140 (68.6)</td>
</tr>
<tr>
<td>ACR70</td>
<td>55 (27.0)</td>
<td>81 (39.7)</td>
<td>94 (46.1)</td>
<td>95 (46.6)</td>
</tr>
<tr>
<td>ACR response categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ACR20 response</td>
<td>63 (30.9)</td>
<td>44 (21.6)</td>
<td>35 (17.2)</td>
<td>36 (17.6)</td>
</tr>
<tr>
<td>ACR20-50</td>
<td>44 (21.6)</td>
<td>35 (17.2)</td>
<td>32 (15.7)</td>
<td>28 (13.7)</td>
</tr>
<tr>
<td>ACR50-70</td>
<td>42 (20.6)</td>
<td>44 (21.6)</td>
<td>43 (21.1)</td>
<td>45 (22.1)</td>
</tr>
<tr>
<td>ACR70</td>
<td>55 (27.0)</td>
<td>81 (39.7)</td>
<td>94 (46.1)</td>
<td>95 (46.6)</td>
</tr>
<tr>
<td>EULAR response criterion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>38 (18.5)</td>
<td>22 (10.7)</td>
<td>19 (9.3)</td>
<td>20 (9.8)</td>
</tr>
<tr>
<td>Moderate response</td>
<td>86 (42.0)</td>
<td>67 (32.7)</td>
<td>65 (31.7)</td>
<td>51 (24.9)</td>
</tr>
<tr>
<td>Good response</td>
<td>81 (39.5)</td>
<td>116 (56.6)</td>
<td>121 (59.0)</td>
<td>134 (65.4)</td>
</tr>
<tr>
<td>DAS28 remission categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3.2</td>
<td>124 (60.5)</td>
<td>89 (43.4)</td>
<td>84 (41.0)</td>
<td>71 (34.6)</td>
</tr>
<tr>
<td>2.6-3.2</td>
<td>27 (13.2)</td>
<td>30 (14.6)</td>
<td>28 (13.7)</td>
<td>27 (13.2)</td>
</tr>
<tr>
<td>&lt;2.6</td>
<td>54 (26.3)</td>
<td>86 (42.0)</td>
<td>93 (45.4)</td>
<td>107 (52.2)</td>
</tr>
<tr>
<td>HAQ MCID</td>
<td>159 (79.1)</td>
<td>175 (86.3)</td>
<td>175 (85.4)</td>
<td>175 (85.4)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise specified. *The mean number of missed work days per week during the recall period by each follow-up visit.

### Table 2: Association between achievement of clinical response and work stoppage and work absence

<table>
<thead>
<tr>
<th>Response criteria</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR response criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>0.30 (0.15-0.61)**</td>
<td>0.53 (0.32-0.90)**</td>
</tr>
<tr>
<td>ACR50</td>
<td>0.29 (0.14-0.60)**</td>
<td>0.54 (0.34-0.86)**</td>
</tr>
<tr>
<td>ACR70</td>
<td>0.22 (0.09-0.56)**</td>
<td>0.41 (0.27-0.62)**</td>
</tr>
<tr>
<td>ACR response categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ACR20 response</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ACR20-50</td>
<td>0.57 (0.23-1.43)</td>
<td>0.68 (0.38-1.25)</td>
</tr>
<tr>
<td>ACR50-70</td>
<td>0.42 (0.17-1.07)*</td>
<td>0.64 (0.36-1.15)</td>
</tr>
<tr>
<td>ACR70</td>
<td>0.14 (0.05-0.40)**</td>
<td>0.30 (0.16-0.55)**</td>
</tr>
<tr>
<td>EULAR response criterion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate response</td>
<td>0.48 (0.20-1.16)</td>
<td>0.51 (0.27-0.98)**</td>
</tr>
<tr>
<td>Good response</td>
<td>0.17 (0.07-0.45)**</td>
<td>0.30 (0.16-0.58)**</td>
</tr>
<tr>
<td>DAS28 remission categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3.2</td>
<td>0.38 (0.12-1.22)</td>
<td>0.53 (0.28-1.00)**</td>
</tr>
<tr>
<td>2.6-3.2</td>
<td>0.27 (0.11-0.62)**</td>
<td>0.50 (0.33-0.77)**</td>
</tr>
<tr>
<td>HAQ MCID</td>
<td>0.44 (0.20-0.98)**</td>
<td>0.64 (0.36-1.14)**</td>
</tr>
</tbody>
</table>

aFrom logistic GEEs model controlling for age, gender, ethnicity, working full time, treatment and some baseline clinical and quality of life outcomes selected by the QIC. *0.05 < P < 0.1; **P < 0.05. OR: odds ratio.
might not be enough to prevent them from work stoppage or work absence. Treatments leading to clinical remission or major improvement are likely to be needed to significantly impact work outcomes. Although this article was not intended to directly measure the treatment effect on work outcomes among patients with early RA, the results showed that treatment with ETN+MTX was associated with reduced likelihood of work stoppage or work absence, consistent with our previous report [6].

It is worth noticing that the adjusted odds ratios of work stoppage (0.44) among the group with DAS-28 =2.6-3.2 compared with the group with DAS-28 >3.2 appear identical to that among the DAS-28 remission group compared with the group with DAS-28 >3.2 (0.46), although there are minor differences in the CIs so that one is significant and the other is not. This is probably due to the small number of patients whose DAS-28 was between 2.6 and 3.2. Therefore, it needs further investigation on whether achieving low-disease activity (DAS-28 =2.6-3.2) is also associated with improved work outcomes.

Several previous studies have addressed the link between response and work outcomes, but these study findings might not be comparable due to their different definitions of work outcomes and/or response criteria. In the study by Zhang et al. [9], no significant difference in improvement of absenteeism at 12 weeks from baseline was found between responders and non-responders according to ACR20 and MCID of HAQ. Using a similar method to Zhang et al., Osterhaus et al. [10] found a significant difference in improvement in absenteeism at 24 weeks from baseline between responders and non-responders. These two studies may not be comparable with our study because our outcome was the occurrence of work absence, whereas both Zhang et al. and Osterhaus et al. used the number of missed work days as their main outcome.

In the study by Halpern et al. [11], a significant association was found between ACR20 response and work stoppage, which is also in contrast with our findings. However, the odds ratio of stopping work among patients in DAS-28 remission relative to those with no remission was significant in Halpern et al.’s study. In our study, patients achieving DAS-28 remission were significantly less likely to stop work than those with DAS-28 >3.2, but not in those with DAS-28 between 2.6 and 3.2. The difference in findings between our study and previous studies may also be partially attributed to the fact that our study population was early RA patients, whereas previous studies were related to patients with long-standing RA.

Among early RA patients, Puolakka et al. [12] found significant differences in the cumulative duration of work disability per patient-observation year among patients achieving remission, ACR50 but no remission, ACR20 but not ACR50 compared with those not achieving ACR20. Our study did not find significant differences in the odds of work absence or stoppage between ACR20–ACR50, ACR50–ACR70 and no ACR20 response. Different response categorization and outcome definition may contribute to the different findings between our study and that of Puolakka et al.

A limitation of this study is that in the COMET trial, patients were asked about their work stoppage and work absence since last visit. In this study, we assumed the last visit was the last clinical visit and thus the recall period was the prior 4 weeks for visits at Weeks 12 and 24 and prior 8 weeks for visits at Weeks 36 and 52. Longer recall periods may decrease the accuracy of responses. It is likely that the number of days of missed work will be reported less accurately relative to occurrences of missed work. In addition, the trial did not collect information on education and job characteristics, and therefore we were not able to adjust for these variables. A recent systematic literature review showed that there is strong evidence that education and job characteristics predict work disability in RA [20]. However, no evidence is available to show that there are any associations between education or job characteristics and clinical responses, which suggests that they are not likely to be confounders. Therefore, the association between clinical responses and work stoppage and work absence would probably not be much affected by including education or job characteristics in our models.

Furthermore, due to the small number of patients reporting work absence days ≥0 and the high proportion of patients reporting work absence days =0, we did not use the number of days of work absence as the outcome. Instead, our outcome was defined as work absence dichotomized as present or absent, which treats 1 day of work absence as the same as ≥20 days. Studies with larger samples are required to further measure the association between clinical responses and the magnitude of work outcomes.

In conclusion, employed patients with early RA achieving a robust clinical response are less likely to stop working or miss work. The association was significant only among patients who achieved high response levels such as the ACR70 and DAS-28 remission. This suggests that achieving clinical remission or major improvement might be necessary to significantly impact work outcomes.

**Rheumatology key messages**

- Patients with early RA achieving robust clinical responses are less likely to stop/miss work.
- Achieving clinical remission or major improvement might be necessary to significantly impact work outcomes.

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References


